LEADING ARTICLE

An update on the role of irreversible electroporation in locally advanced pancreatic adenocarcinoma

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Significant treatment challenges remain in near 40% of patients who are diagnosed with stage III locally advanced pancreatic adenocarcinoma. Current standard of care literature has outlined a median overall survival in this sub group of patients of 12–15 months in most current reviews.[1,2] The use of pancreatic ablation has been reported initially with thermal based modalities such as radiofrequency and microwave and more recent stereotactic body radiotherapy modalities with wide ranging results. The morbidity and mortality associated with such treatments has been significant with rates of 50% and 10% reported respectively.[3]

The initial evaluation of the use of irreversible electroporation as a potential non thermal injury based ablative appeared promising.[4,5] The use of electroporation has been well-established over the last 20–30 years with the insertion of proteins, small molecules, and even cell fusion. However the utilization of irreversible electroporation as a primary oncology ablative therapy has only recently been reported since 2008. The ability to achieve irreversible electroporation is based on inducing permanent cell porosity and at least 1000 V of electrical energy to induce electrolyte imbalance of calcium into the cell and sodium out of the cell to lead to permanent cell death through apoptosis over an 8–10 week period of time.[6,7]

Initial long term animal survival data has confirmed the safety of the use of IRE with a lack of vascular thrombosis and the safety of IRE around major portal structures.[8,9] Similar work has confirmed that the IRE energy stays within a non thermal injury temperature as long as there is appropriate spacing and IRE electrode probe exposure.[10] Similar safety data has also demonstrated the inability to utilize IRE around metal stents and potentially metal fiducial markers because of the significant conductive electrical energy that is achieved. Lastly, preclinical models have confirmed the concern around using IRE as a debulking therapy because of the potential inflammatory and immune mediated upregulation that could stimulate the residual non treated tumor and potentially increase tumour growth.[11]

Clinical data has been confirmed to demonstrate both a 90 day safety and improvement in overall survival when compared to chemo and radiation therapy alone.[12,13] It is also important to understand that a significant learning curve exists to achieve optimization of the technique. Most recently a prospective review of 200 patients who underwent IRE for locally advanced pancreatic cancer demonstrated improvement in overall survival with a median survival of 25 months.[14] This benefit is survival extended to both patients who were treated with IRE alone "in-situ" as well as in those who underwent resection for locally advanced pancreatic cancer and IRE was used for margin accentuation.[14]

Concerns still remain with the use of IRE in locally advanced pancreatic cancer predominantly around optimal patient selection, end user ultrasound, technical ability, and standardization of the IRE energy delivery. It is critical that both current users and new users follow the established patient selection safety and ethicacy algorithms that have been published in large patients series.[15,16] Clearly the technical demand for needle placement utilizing high quality ultrasound imaging for precise IRE electrode bracketing is the single greatest challenge for current and future expanded indication for IRE use.[16,17] Given these concerns all current users have an ethical obligation to consider collaborating in prospective patient registries (ClinicalTrials.gov Identifier: NCT02674100) so that more real-time and immediate quality parameters can be assessed. This would allow re-education and technical changes to be implemented efficiently while minimizing patient harm.

The use of IRE alone as a solitary ablative therapy is just the beginning of potential applications. The concept of electro-chemotherapy, a combination of IRE with chemotherapy is being rapidly evaluated. In additional the optimization and utilization of IRE for controlled immune mediated enhancement is also of a potentially optimistic therapy in patients at their initial stage in diagnosis.[18]

Thus IRE is a technique that has been technically optimized. It is a safe and effective therapy when appropriate patient selection is utilized. IRE should not be and will not be successful as a salvage therapy. For example in patients who have already gone

through extensive surgical dissection are not suitable candidates given that the surgical planes have been disrupted IRE will not be able to be effectively utilized. Similarly IRE should be used with caution after high dose radiation therapy because of the significant damage that the radiation therapy induces and the inability for reparative effects after IRE to be obtained. The keys to sustainability with use of this therapy are to maintain the standards of use with regard to needle placement and energy delivery in well-selected patients with stage III locally advanced adenocarcinoma.

Conflicts of interest

RCGM is a paid consultant for Angiodynamics.

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